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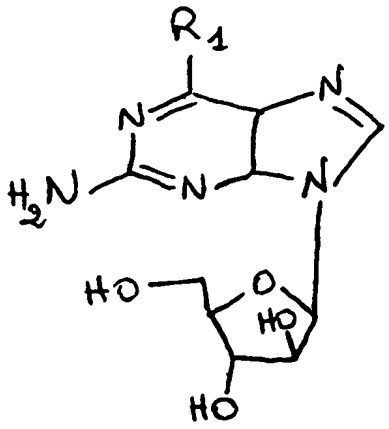
(54) Title: METHOD FOR TREATING B-CELL TUMORS WITH ARA-G NUCLEOSIDE DERIVATIVES

(57) Abstract

The present invention relates to the treatment of B-cell lineage tumours (such as acute or chronic lymphocitic leukemias, acute or chronic myelogenous leukemias or Hodgkin's or non Hodgkin's lymphomas) using arabinofuranosyl purine (ara-G) derivatives of formula (I), wherein R_1 is a C_{1-5} alkoscy or a pharmaceutically acceptable derivative thereof (such as compounds esterified or derivatized on the sugar residue). These compounds can also be used in combination with a second therapeutic agent such as sludarabine for the same use(s).



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METHOD FOR TREATING B-CELL TUMORS WITH ARA-G NUCLEOSIDE DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to the activity of certain arabinofuranosyl purine derivatives in treating tumors of B-cell lineage.

BACKGROUND OF THE INVENTION

Cancers are the second most frequent cause of death in children, and leukemia is the most common neoplasm in children. (*Clinical Oncology*, P. Rubin, ed., W.B. Saunders Company, Philadelphia, 1993). There are six new cases per 100,000 subjects per year. (Cutter, S.J. et al., *JNCI* 39:993-1026 (1967).

Leukemias are neoplasias in which the two major defects are unregulated proliferation and incomplete maturation of hemopoietic or lymphopoietic progenitors. Leukemia originates in the marrow, although leukemic cells may infiltrate lymph nodes, liver, spleen, and other tissues. The principal clinical manifestation is a decrease of red blood cells, granulocytes, and platelets in the blood as a result of suppression of normal hemopoiesis by the malignant process. In the chronic or well-differentiated leukemias, unregulated proliferation, accumulation of leukemic cells, and elevated white blood count dominate, although differentiation and maturation of the leukemia cells may be largely preserved. In acute leukemias, unregulated proliferation also occurs, but maturation of the leukemic progenitors is profoundly impaired. Therapy of chronic leukemias is directed toward suppressing the excessive proliferation to reduce the accumulation of leukemic cells and to permit improvement in effective

hemopoiesis, whereas in acute leukemias intensive treatment is used to obliterate the leukemic clone.

Acute lymphocytic leukemia (ALL) is regarded as a proliferation and accumulation of lymphoblasts originating in marrow and perhaps in extramyeloid lymphatic tissue. The disease can originate in lymphoid cells of different lineages, thus giving rise to B-cell or T-cell leukemias or sometimes to mixed lineage leukemia (Cortes, J.E. et al.. *Cancer* 76(12):2393-2417, 1995). The normal homologue of the leukemic lymphoblasts is not known. It is probable that the lesion is present in a primitive lymphoid progenitor cell pool, that may be placed at a pre-B-cell level of lymphopoiesis in most cases. The most frequent manifestations of ALL result from the reduction of normal hemopoietic cells. Accumulation of leukemic blast cells in peripheral tissues may occasionally lead to symptoms referable to specific sites or organs. The classification of ALL is based on the immunologic characteristic of lymphoblasts. About 20% of ALL cases have T-cell markers and 80% have B-cell characteristics.

Nearly 70% of ALL cases in children and about 60% of ALL cases in adults fall into the early pre-B acute lymphoblastic leukemia category. The immunophenotype is characterized by lack of expression of cytoplasmic or surface immunoglobulins. Pre-B-cell acute lymphoblastic leukemia is defined by the expression of cytoplasmic immunoglobulin heavy chains. It represents approximately 20% of all cases of ALL. Other subtypes include transitional pre-B-cell acute lymphoblastic leukemia, mature B-cell acute lymphoblastic leukemia and T-cell acute lymphoblastic leukemia.

Chronic lymphocytic leukemia (CLL) is a disorder in which increased proliferation of mature lymphocytes and prolonged survival of mature lymphocytes can lead to an enormous accumulation of lymphocytes in marrow, blood, lymph nodes, liver, and spleen. The disorder may originate in marrow lymphoid tissue; however, abnormal proliferation

also occurs in lymph nodes and spleen. About 95% of the cases of CLL have leukemic lymphocytes whose phenotype is that of B lymphocytes. The precise level of differentiation at which the leukemic lesion originates is unknown. It probably is at a level that corresponds to the common lymphopoietic progenitor cell, since a T-cell surface antigen CD5 may be present on a high proportion of CLL cells, despite their dominant phenotypic expression of B-cell markers, including immunoglobulin. Acquired abnormalities of T-cell function that appear later in the disease course may be important in pathogenesis. It has been suggested that excessive suppressor activity by T cells limits the immunoglobulin response of residual normal B cells in CLL, eventually leading to hypogammaglobulinemia. In later disease stages, T-cell function may be depressed by large accumulations of B cells or by an intrinsic defect.

Diffuse involvement of marrow and the presence of large numbers of circulating pathologic lymphocytes may accompany any histopathologic type of lymphoma. This pattern is seen most frequently with nodular, poorly-differentiated lymphoma. When leukemia develops in the course of previously diagnosed lymphoma, it indicates disease progression. If lymphoma cell leukemia represents the initial presentation of a lymphoproliferative disorder, it often may be distinguished from classical ALL or CLL by the clinical features of the case and the morphology of the cells. Most lymphoma cells express phenotypes of B lymphocytes.

Hairy cell leukemia is manifested most commonly by bicytopenia or pancytopenia in 80% of cases and splenomegaly in 90% of cases. The diagnosis is made by the identification in either blood, marrow, or spleen of a mononuclear cell with lymphocytic or histiocytic morphology and villous cytoplasmic projections as well as B-cell lymphoid immunologic markers.

A manifestation of acute myelogenous leukemia (AML) is the absence of sufficient normal hemopoietic activity to maintain blood cell counts. In

addition, less common disease manifestations may relate to the accumulation of leukemic blast cells in blood vessels and tissues.

Chronic myelogenous leukemia (CML), like AML and other myelodysplastic syndromes, is a result of an abnormality in the hemopoietic stem cell pool, which in this case results in the accumulation of mostly mature or nearly mature granulocytic cells and often of megakaryocytes. Erythropoiesis is usually impaired. CML may result from a disorder in cell maturation with synchronous development of the cytoplasm and nucleus. Median survival in CML is about 3 1/2 years.

Hodgkin's disease constitutes 40% of malignant lymphomas (*Clinical Oncology*, P. Rubin, ed., W.B. Saunders Company, Philadelphia, 1993). Patients with congenital immunodeficiency disease have an increased risk for developing Hodgkin's disease. Similarly, it occurs more frequently in patients with acquired immune deficiency syndromes, including AIDS. An increased incidence of Hodgkin's disease is seen in patients with elevated titers of various antibodies to the Epstein-Barr virus (EBV), and such elevations recently have been shown to predate the diagnosis of Hodgkin's disease. The cell that confers the malignancy is unknown, but may be the Reed-Sternberg cell, B- or T-lymphocytes, monocytes or macrophages, interdigitating or dendritic reticulum cells, and progenitors of granulocytes. The typical presentation for patients with Hodgkin's disease is one of painless lymph node enlargement. Contiguous growth of tumor into adjacent organs, and lymphatic spread or hematogenous dissemination to retroperitoneal nodes, spleen, liver, bone, or bone marrow will eventually occur if the disease is not treated.

Non-Hodgkin's lymphoma (NHL) is thought to arise from lymphocyte precursors in the bone marrow and thymus rather than immunocompetent lymphoid cells capable of participating in an immune response. These cells undergo specific and irreversible rearrangements of their immunoglobulin genes (B cells) or T-cell receptor genes (T cells) as

they are committed to a specific lineage. T-cell types include lymphoblastic lymphomas, adult T-cell leukemia/lymphoma, mycosis fungoides, Sezary's syndrome, angiocentric immune lesions, and peripheral T-cell lymphomas. B-cell types include small, noncleaved lymphomas, which include Burkitt's and non-Burkitt's subtypes. Most large cell lymphomas are of B-cell phenotype. Surface immunoglobulins and B-cell specific antigens are expressed by these cells. Other types of B-cell lineage include the small lymphocytic well-differentiated lymphomas, the intermediate or small cleaved cell (mantle zone) lymphocytic lymphomas, and the follicular lymphomas.

Multiple myeloma is a neoplastic proliferation of plasma cells characterized by lytic bone lesions, anemia, and serum/urinary monoclonal globulin elevations. The resulting spectrum of clinical disease includes both localized and disseminated forms, which can behave in an indolent or aggressive manner. Multiple myeloma has traditionally been considered a terminally differentiated B-cell malignancy.

It has been reported (*Blood*, 61 (1983), 660; *J. Clin. Ivest.* 74, (1984), 951 and *Cancer Research*, 45 (1985), 1008) that arabinofuranosyl guanine (ara-G) selectively inhibits the growth of T cells compared to B cells and possesses a selective cytotoxic activity for T-leukemic cells. Ara-G is metabolized to ara-GTP, which inhibits DNA synthesis. The selective toxicity of ara-G for T cells is attibuted to decreased catabolism of ara-GTP in T cells as compared to B cells (Fridland, A. et al., *Proc. Soc. Exp. Biol. Med.*, 179:456-462, 1985; Verhoef, V. et al., *Cancer Res.*, 45:3646-3650, 1985). Thus, T cells have a greater exposure to ara-GTP than do B cells. Ara-G has been proposed as a putative chemotherapeutic or immunosuppressive agent, but its poor solubility and low bioavailability render its administration impractical.

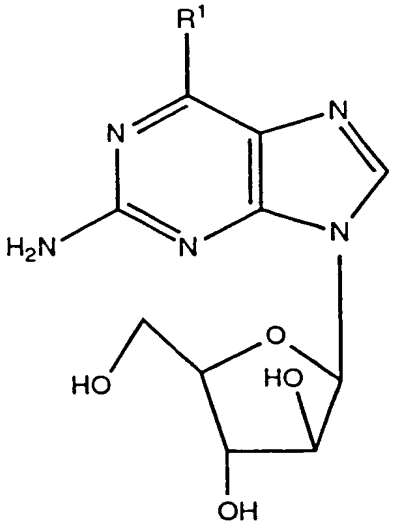
U.S. Patent No. 5,492,897 discloses that certain purine arabinosides are useful as antitumor agents, and are particularly useful in the treatment of

T-cell lymphoproliferative disorders such as lymphocytic leukemia, malignant lymphoma, autoimmune diseases, and as immunomodulators. In particular, 9-ß-D-arabinofuranosyl-2-amino-6-methoxy-9H-purine, a compound which is enzymatically converted to ara G in the host, can be used in the treatment of T-cell lymphoblastic leukemia.

It has now surprisingly been discovered that 9-ß-D-arabinofuranosyl-2-amino-6-methoxy-9H-purine can be used to treat cancers of B-cell lineage. This was unexpected, as the mechanism for the activity of 9-ß-D-arabinofuranosyl-2-amino-6-methoxy-9H-purine in the treatment of T-cell disease is the reduced ability of T-cells to catabolize ara-GTP, as compared to B-cells.

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, in a first aspect of the present invention, there is provided a method of treatment of tumors of B-cell lineage in mammals, including humans, which comprises administering to the mammal an effective amount of a compound of formula (I)



(I)

wherein R^1 is a C_{1-5} alkoxy group or a pharmaceutically acceptable derivative thereof. Suitably R^1 is methoxy or ethoxy and preferably a methoxy group.

In a further aspect, the present invention provides the use of a compound of formula (I) as defined above, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment of tumors of B-cell lineage. Suitably R^1 is methoxy or ethoxy and preferably a methoxy group.

The term "effective amount" refers to an amount effective in treating tumors of B-cell lineage in a patient either as monotherapy or in combination with other agents. The term "treating" or "treatment"as used herein refers to the alleviation of symptoms of a particular disorder in a patient or the improvement of an ascertainable measurement associated with a particular disorder and is intended to include prophylaxis. As used herein, the term "patient" refers to a mammal, including a human.

The term "pharmaceutically acceptable derivative" or "pharmaceutically acceptable prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of the present invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an active metabolite or residue thereof. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of the invention when such compounds are administered to a mammal (e.g. by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g. the brain or lymphatic system) relative to the parent species.

The term "tumor(s) of B cell lineage", as used herein, refers to tumor(s) that may, by their immunologic and clinical characteristics, be determined to have B cell involvement.

The compounds of the present invention may be used in the treatment of tumors of B-cell lineage, including, but not limited to, ALL, CLL, CML, AML, hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, and multiple myeloma.

Preferred derivatives of compounds of the invention include mono-, di- or tri-esters of the arabino-sugar residue substituted at the 2'-, 3'-, and 5'-positions of said residue.

Such preferred esters include carboxylic acid esters in which the non-carbonyl moiety of the ester grouping is selected from straight or branched chain alkyl (e.g. n-propyl, t-butyl, n-butyl), alkoxyalkyl (e.g. methoxymethyl), aralkyl (e.g. benzyl), aryloxyalkyl (e.g. phenoxymethyl), aryl (e.g. phenyl) optionally substituted by halogen, C_{1-4} alkyl or C_{1-4} alkoxy, nitro or amino; sulphonate esters such as alkylsulphonyl; or alkylarylsulphonyl (e.g. methanesulphonyl or tosylsulphonyl); dicarboxylic acid esters (e.g. succinyl) or C_{1-4} alkyl esters thereof; amino acid esters (e.g. L-valyl); and mono-, di- or tri-phosphate esters. Pharmaceutically acceptable salts of these ester include sodium, potassium, NR_4^+ where R = H or C_{1-6} alkyl, halides and acid addition salts. In the above ester group, the alkyl groups (including those in alkoxy groupings) contain 1 to 12 carbon atoms and the aryl groups are preferably phenyl.

Preferred esters of the present invention include:

2-amino-6-methoxy-9-(5-O-propionyl-β-D-arabinofuranosyl)-9H-purine,

2-amino-9-(5-O-butyryl-β-D-arabinofuranosyl)-6-methoxy-9H-purine,

2-amino-6-methoxy-9-(3-O-pivaloyl-β-D-arabinofuranosyl)-9H-purine,
2-amino-6-methoxy-9-(2-O-valeryl-β-D-arabinofuranosyl)-9H-purine,
2-amino-9-(3-O-benzoyl-β-D-arabinofuranosyl)-6-methoxy-9H-purine,
2-amino-6-methoxy-9-(2-O-pivaloyl-β-D-arabinofuranosyl)-9H-purine,
2-amino-9-(2-O-benzoyl-β-D-arabinofuranosyl)-6-methoxy-9H-purine,
2-amino-6-methoxy-9-(5-O-valeryl-β-D-arabinofuranosyl)-9H-purine,
(5-O-acetyl-β-D-arabinofuranosyl)-2-amino-6-methoxy-9-9H-purine,
2-amino-6-methoxy-9-(5-O-(4-methoxy-4-oxobutyryl)-β -D-arainofuranosyl)-9H-purine,
9-(3,5,-di-O-acetyl-β-D-arabinofuranosyl)-2-amino-6-methoxy-9H-purine,
9-(2,5-di-O-acetyl-β-D-arabinofuranosyl)-2-amino-6-methoxy-9H-purine,
9-(2-O-acetyl-β-D-arabinofuranosyl)-2-amino-6-methoxy-9H-purine,
9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)-2-amino-6-methoxy-9H-purine,
2-amino-9-(5-O-isobutyl-β-D-arabinofuranosyl)-6-methoxy-9H-purine,
9-(2,3-di-O-acetyl-β-D-arabinofuranosyl)-2-amino-6-methoxy-9H-purine,
2-amino-6-methoxy-9-(5-O-valyl-β-D-arabinofuranosyl)- 9H-purine,
2-amino-6-methoxy-9-(5-O-methylsuccinyl-β-D-arabinofuranosyl)-9H-purine, and
2-amino-6-methoxy-9-(5-O-valeryl-β-D-arabinofuranosyl)-9H-purine.

Treatment of neoplastic growth with a compound of the present invention may involve the administration of the compound alone or in combination with other drugs as a preparatory regimen intended to cause bone marrow ablation prior to autologous or allogeneic cord blood transplantation, peripheral blood stem cell transplantation, or bone marrow transplantation for leukemia, lymphoma, myeloma, or other malignancies, for example in an analogous manner to the administration of high doses of busulfan and cyclophosphamide prior to bone marrow

transplantation for acute leukemia. (Santos, G.W., bone Marrow Transplant, 1989 Jan 4 suppl. 1, 236-9).

A compound of the present invention may also be used to treat blood or bone marrow ex vivo to remove malignant stem cells, in an analogous manner to that described for 4-hydroperoxycyclophosphamide by Yeager, A.M. et al., N. Engl. J. Med.., Jul 17, 1986, 315 (3), 141-7.

A compound of the present invention and their pharmaceutically acceptable derivatives may be employed in combination with other therapeutic agents for the treatment of the above-mentioned diseases or conditions. Combination therapies according to the present invention comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered simultaneously in either the same or different pharmaceutical formulations or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Preferably the combination therapy involves the administration of one compound according to the invention and one of the agents mentioned herein below.

Examples of such further therapeutic agents include agents that are effective for the treatment of tumors or associated conditions are chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, aziridines, thiotepa, busulfan, nitrosureas, carmustine, lomustine, streptozocin, altretamine, dacarbazine, procarbazine, carboplatin, cisplatin, oxaliplatin, fluorouracil, floxuridine, methotrexate, leucovorin, hydroxyurea, thioguanine, mercaptopurine, cytarabine, pentostatin, fludarabine, fludarabine phosphate, cladribine, asparaginase, and gemcitabine.

The compounds of the present may be made according to European Patent Application No. 294114 and U.S. Patent No. 5,492,897, incorporated herein by reference hereto.

The esters of the present invention may be made according to U.S. Patent No. 5,492,897, which is incorporated herein by reference hereto.
The compounds according to the invention, also referred to herein as the active ingredient, may be administered for therapy by any suitable route including oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intrathecal, intradermal, intraarterial, and intravitreal). It will be appreciated that the preferred route will vary with the condition and age of the recipient, the nature of the infection and the chosen active ingredient.

In general a suitable dose for each of the above-mentioned conditions will be in the range of 0.01 to 500 mg per kilogram body weight of the recipient (e.g. a human) per day, particularly in the range 1.0 to 250 mg per kiogram body weight per day. Unless otherwise indicated, all weights of active ingredient are calculated as the parent compound of formula (I); for salts or esters thereof, the weights would be increased proportionally. The desired dose may be presented as one, two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. In some cases the desired dose may be given on alternative days. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1000 mg or 50 to 500 mg, preferably 20 to 500 mg, and most preferably 100 to 400 mg of active ingredient per unit dosage form.

While it is possible for the active ingredient to be administered alone it is preferable to present it as a pharmaceutical formulation. The formulations of the present invention comprise at least one active ingredient, as defined above, together with one or more acceptable carriers

therof and optionally other therapeutic agents. Each carrier must be "acceptable" in the sense of being compatible with the other ingreadients of the formulation and not injurious to the patient.

Formulations include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intraarterial, and intravitreal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

The present invention further includes a pharmaceutical formulation as hereinbefore defined wherein a compound of formula (I) or a pharmaceutically acceptable derivative thereof and at least one further therapeutic agent are presented separately from one another as a kit of parts.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aquesous solution or 2) dissolved and/or dispersed in an adhesive or 3) dispersed in a pollymer. A suitable concentration of the active compound is about 1% to 25%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by electrotransport or iontophoresis as generally described in Pharmaceutical Research 3 (6), 318 (1986).

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored any may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in molds.

Formulations suitable for parenteral administration include aqueous and nonaqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation compatible with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or daily subdose of the active ingredients, as hereinbefore recited, or an appropriate fraction thereof.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way. "Active ingredient" denotes a compound of formula (I) or multiples thereof or a physiologically functional derivative of any of the aforementioned compounds.

Example 1: Tablet Formulation

The following formulations A, B and C are prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of magnesium stearate and compression.

Formulation A

	mg/tablet
Active Ingredient	250
Lactose B.P.	210
Povidone B.P.	15
Sodium Starch Glycollate	20
Magnesium Stearate	5
	500

Formulation B

	mg/tablet
Active Ingredient	250
Lactose B.P.	150

Avicel PH 101	60
Povidone B.P.	15
Sodium Starch Glycollate	20
Magnesium Stearate	5

	500

Formulation C

	mg/tablet
Active Ingredient	250
Lactose B.P.	200
Starch	50
Povidone	5
Magnesium Stearate	4

	359

The following formulations, D and E, are prepared by direct compression of the admixed ingredients. The lactose in formulation E is of the direct compression type (Dairy Crest-"Zeparox").

Formulation D

	mg/tablet
Active Ingredient	250
Pregelatinized Starch NF15	150

	400

Formulation E

	mg/tablet

Active Ingredient	250
Lactose B.P.	150
Avicel	100
	500

Formulation F (Controlled Release Formulation)

The formulation is prepared by wet granulation of the ingredients with a solution of povidone followed by the addition of magnesium stearate and compression.

	mg/tablet
Active Ingredient	500
Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
Lactose B.P.	53
Povidone B.P.	28
Magnesium Stearate	7
	700

Drug release takes place over a period of about 6-8 hours and is complete after 12 hours.

Example 2: Capsule Formulations

Formulation A

A capsule formulation is prepared by admixing the ingredients of formulation D in Example 1 above and filling into a two-part hard gelatin capsule. Formulation B (infra) is prepared in a similar manner.

Formulation B

	mg/capsule
Active Ingredient	250
Lactose B.P.	143
Sodium Starch Glycollate	25
Magnesium Stearate	2
	420

Formulation C

	mg/capsule
Active Ingredient	250
Macrogel 4000 B.P.	350
	600

Capsules of formulation C are prepared by melting the Macrogel 4000 B.P., dispersing the active ingredient in the melt and filling the melt into a two-part hard gelatin capsule.

Formulation D

	mg/capsule
Active Ingredient	250
Lecithin	100
Arachis Oil	100
	450

Capsules of formulation D are prepared by dispersing the active ingredient in the lecithin and arachis oil and filling the dispersion into soft, elastic gelatin capsules.

Formulation E (Controlled Release Capsule)

The following controlled release capsule formulation is prepared by extruding ingredients a,b, and c using an extruder, followed by spheronization of the extrudate and drying. The dried pellets are then coated with release-controlling membrane (d) and filled into a two-piece, hard gelatin capsule.

		mg/capsule
(a)	Active Ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose B.P.	125
(d)	Ethyl Cellulose	13
		513

Example 3: Injectable Formulation

Formulation A

	kg
Active Ingredient	2.0
Sodium Chloride	1.8
Hydrochloric Acid Solution 0.1 N or Sodium Hydroxide Solution 0.1 N q.s. to pH	5.5-6.5
Water for Injection	q.s.
Total	400.0 liters

Approximately 380 kg of water for injection (40°-50° C) is collected in a jacketed stainless steel or other suitable manufacturing vessel equipped with a suitable mixer. The sodium chloride is added to the manufacturing

vessel and mixed. The active ingredient is added and mixed for not less than 5 minutes or until the active ingredient is dissolved. If the pH of the solution at approximately 25° C is outside the range 5.5 to 6.5, then it is adjusted to 6.0 with either 0.1 N hydrochloric acid solution and/or 0.1 N sodium hydroxide solution. If necessary, the final batch weight is adjusted to 401.9 kg (400.0 liters) with water for injection (40°-50° C) and mixed for not less than 5 minutes. The solution is filtered through a suitable sterile 0.22 μM, or equivalent, membrane filter into a sterile jacketed stainless steel or other suitable sterile vessel. The solution (52 g, ± 2%) is aseptically filled into sterile 50 mL flint glass vials. Sterile closures are aseptically inserted, the overseals applied, and the vials are sterilized.

Formulation B

Active Ingredient	125 mg
Sterile, Pyrogen-free, pH 7 Phosphate Buffer, q.s. to	25 ml

Formulation C Lyophilized Formulation

Active Ingredient [a]	0.279 kg
1 N Hydrochloric Acid Solution and/or 1 N Sodium Hydroxide Solution to	pH 5.0-7.5
Water for Injection [b]	q.s.
Total	35.0 kg [c]

[a] This is the theoretical weight. The actual weight is calculated from a factor for each lot.

[b] Removed during processing.

[c] Based on a specific gravity of 1.0027.

Approximately 31 kg of water for injection (30°-40° C) is collected in a jacketed stainless steel or other suitable manufacturing vessel equipped with a suitable mixer. A water sample from the manufacturing vessel is collected and submitted for bacterial endotoxins testing. When the test result is negative, the active ingredient is added to the manufacturing vessel and mixed for not less than five minutes or until the active ingredient is dissolved. The final batch weight is adjusted to 35.0 kg with water for injection (20° -30° C) and mixed for not less than 5 minutes. The pH of the solution is adjusted to 6.0 (range 5.0 to 7.5), if necessary, with either 1 N hydrochloric acid solution and/or 1 N sodium hydroxide solution. The solution is filtered under pressure through a suitable sterile 0.22 micrometer or equivalent membrane filter into a sterile jacketed stainless steel or other suitable sterile vessel. Approximately 25 mL of the solution is aseptically filled into sterile 50 mL amber glass vials, the sterile lyophilizing closures are partially inserted, and the solution is lyophilized. The closures are completely inserted and the overseals are applied.

Example 4: Intramuscular Injection

Active Ingredient	200 mg
Benzyl Alcohol	0.10 g
Glycofurol 75	1.45 g
Water for injection q.s. to	3.00 ml

The active ingredient is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml amber glass vials (type 1).

Example 5: Syrup

Active Ingredient	250 mg
Sorbitol Solution	1.50 g
Glycerol	2.00 g
Sodium Benzoate	0.005 g
Flavor, Peach 17.42.3169	0.0125 ml
Purified Water q.s. to	5.00 ml

The active ingredient is dissolved in a mixture of the glycerol and most of the purified water. An aqueous solution of the sodium benzoate is then added to the solution, followed by addition of the sorbital solution and finally the flavor. The volume is made up with purified water and mixed well.

Example 6

Patient no. 1009-32 was diagnosed with recurrent acute lymphoblastic leukemia (precursor B cell type). The bone marrow aspirate contained 54% lymphoblasts.

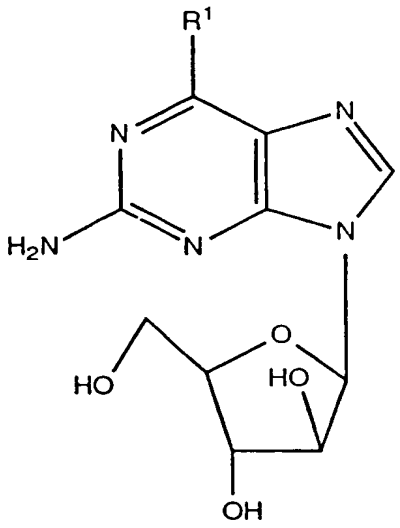
The patient received 60 mg/kg of 9-ß-D-arabinofuranosyl-2-amino-6-methoxy-9H-purine (code name 506U78) once daily for five days (12/18/95 to 12/22/95). On 1/22/96 the bone marrow aspirate contained 9% blasts, consistent with partial response to therapy.

CLAIMS

The application of which this description and claims form part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims.

We claim:

1. A method of treating tumors of B-cell lineage in a mammal which comprises administering to said mammal an effective B-cell lineage tumor treatment amount of a compound of formula (I)



(I)

wherein R^1 is a C_{1-5} alkoxy group or a pharmaceutically acceptable derivative thereof.

2. The method of claim 1 wherein R^1 is methoxy.

3. The method of claim 1 wherein the compound is 9-ß-D-arabinofuranosyl-2-amino-6-methoxy-9H-purine.

4. The method of claim 1 wherein the pharmaceutically acceptable derivative is (5-O-acetyl-β-D-arabinofuranosyl)-2-amino-6-methoxy-9-9H-purine.

5. The method of claim 1 wherein the B-cell lineage tumor is selected from the group consisting of leukemia, lymphoma and myeloma.

6. The method of claim 5 wherein the leukemia is acute lymphocytic leukemia.

7. The method of claim 5 wherein the leukemia is chronic lymphocytic leukemia.

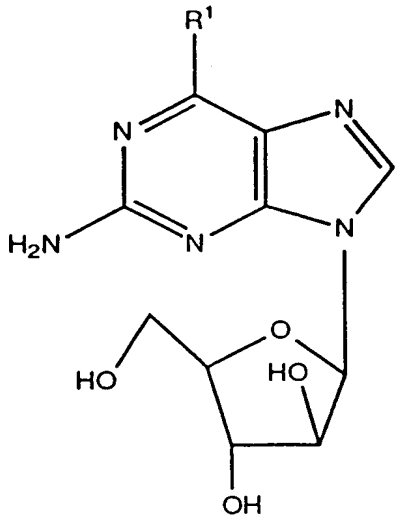
8. The method of claim 5 wherein the leukemia is acute myelogenous leukemia.

9. The method of claim 5 wherein the leukemia is chronic myelogenous leukemia.

10. The method of claim 5 wherein the lymphoma is Hodgkin's disease.

11. The method of claim 5 wherein the lymphoma is non-Hodgkin's lymphoma.

12. A method of treating tumors of B-cell lineage in a mammal which comprises administering to said mammal an effective B-cell lineage tumor treatment amount of a compound of formula (I)



(I)

wherein R^1 is a C_{1-5} alkoxy group or a pharmaceutically acceptable derivative thereof in combination with a suitable second therapeutic agent.

13. The method of claim 12 wherein R^1 is methoxy and the suitable second therapeutic agent is fludarabine.

INTERNATIONAL SEARCH REPORT

Int ational Application No
PCT/US 98/05771

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/70

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARBUCK ET AL.: "New drugs in non-Hodgkin's lymphoma" ANALS OF ONCOLOGY, vol. 8, 5 - 8 June 1996, 6TH INT CONF ON MALIGNANT LYMPHOMA, LUGANO, SWITZERLAND, pages 119-128, XP002071340 Suppl.1, 1997 see page 119 - page 121	1-3,5,6
A	---	11-13
X	RODRIGUEZ ET AL.: "Differential metabolism of arabinosylguanine in T-ALL vs. other leukemias: strategies to increase triphosphate accumulation" PROC ANNU MEET AM ASSOC CANCER RES., vol. 38, March 1997, page 100 XP002071341 see #672	1-8,12, 13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 July 1998	31.07.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In: ıtional Application No
PCT/US 98/05771

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ³	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	HO ET AL.: "Clinical trials using compound 506U78" ONCOLOGY (HUNTINGT), vol. 10, no. 12, December 1996, pages 1831-1832, XP002071342 see page 1831, right-hand column, last paragraph	1-3
A	VERHOEF ET AL.: "Metabolic basis of arabinonucleoside selectivity for human leukemic T- and B-lymphoblasts" CANCER RESEARCH, vol. 45, no. 8, August 1985, pages 3646-3650, XP002071343 see the whole document	1-13
A	FRIDLAND ET AL.: "Metabolism and selectivity of arabinonucleoside in human lymphoid cells" PROC SOC EXP BIOL MED, vol. 179, no. 4, September 1985, pages 456-462, XP002071344 see the whole document	1-11
A	WO 92 01456 A (KRENITSKY ET AL.) 6 February 1992 cited in the application see the whole document & US 5492897 A	1-13
A	WO 94 29312 A (MCMURRY ET AL.) 22 December 1994 see whole document, especially p.30, lines 24-28; p.31, lines 37-38; page 33; pages 38, 39, compounds B.4268 and B.4279; p.41, l. 30-38; p.45, points 6),7)	1-12
P,X	RODRIGUEZ ET AL.: "Pharmacological and biochemical stategies to increase the accumulation of arabinofuranosylguanine triphosphate in primary human leukemia cells" CLINICAL CANCER RESEARCH, vol. 3, no. 11, November 1997, pages 2107-2113, XP002071345 see the whole document	1-13
P,X	KEATING: "Leukemia: a model for drug development" CLINICAL CANCER RESEARCH, vol. 3, no. 12 Pt II, December 1997, pages 2598-2604, XP002071346 see page 2602, right-hand column	1-13

3

INTERNATIONAL SEARCH REPORT

..ernational application No.
PCT/US 98/ 05771

Box I Observations wh re certain claims w re found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 1-13
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/US 98/05771

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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